Judiciary Testimony December 5, 2013

1. Thank you for letting me speak today. I am Steven Sharpe from Jackson MI

2. I am here to support HB5104, Thank you Rep Kowall for the Concentrates bill.

3. I was diagnosed with colon cancer in late 2010 and was told I needed a Colon resection to remove the diseased section. I wanted to do a Cannabis oil treatment on myself. I told my Doctor and Surgeon what I was going to do and they told me I would die if I choose that route. It was a home remedy and would not kill cancer. The standard treatment is 60 grams of oil in 90 days or less. I was told I did not have 90 days and not even 60 days to wait for this to work. I was told it was in the wall of my colon already and was a very aggressive cancer. I started my treatment the day I was informed about my cancer and after only 30+ days of oil, (December 8 of 2010) they removed a section of my colon and it was cancer free to my delight and to the amazement of my Doctor, Surgeon and Pathologist (Pathology reports attached)

4. Concentrates should be available to make, use and share with the patients in Michigan. It is very important to the MMMA program we voted for in 2008, overwhelmingly.

5. Attached is a photo of a Cannabis leaf that is ready to harvest. Inside of the circle is a small ball on top of a clear stem. This is the oil, resin, CBD and THC. This is the only place it happens for Cannabis. The rest is vegetable material and could be used to make baking flour or anything else. This medicine needs to be extracted with something that will adsorb the oil to reduce it to the finest extract and then added

to anything the patients need. When done correctly, each dose will have the same effect for the end user.

6. Concentrate's being ingested last longer then smoking, but takes longer to be activated. Smoking effect's start almost immediately and ingesting takes 45 -90 minutes to take effect.

7. HB 5104 will help so many more people with their medical needs then just smoking, so please include this bill with HB 4271 to get the Provisioning Centers open in Michigan so the patients and caregivers have a safe access to these important medicines made from Cannabis.

8. I have included letters from my patients that I have helped Cannabis Extracts to help improve their health & quality of life. Some of my patients are working through the University of Michigan which needs to be able to handle and administer Cannabis in a controlled setting to show the rest of Michigan that there is something out there that is non- addicting.

9. Thank you for your time today and please support HB 5104 and HB 4271 to get safe access back to those that matter.

Steven Sharpe
535 Gilletts Lake Rd
Jackson Michigan, 49201
517-795-8077
sssharpe2009@gmail.com

RESPIRATORY: No history of chronic cough, hemoptysis, shortness of breath.

GASTROINTESTINAL: No nausea, vomiting, diarrhea, hematochezia.

PHYSICAL EXAMINATION

On physical examination, the patient is a somewhat obese middle aged Caucasian male in no acute distress.

HEENT: Skull is atraumatic, normocephalic. Pupils are equal and reactive to light. Extraocular movements intact. Sclerae clear, not icteric.

LUNGS: Clear.

HEART: Regular rate and rhythm.

ABDOMEN: Soft. Nontender.

EXTREMITIES: Unremarkable.

NEUROLOGICAL: Examination within normal limits.

IMPRESSION:
The patient presents with a sessile polypoid lesion in the sigmoid colon with two separate procedures and biopsies demonstrating adenocarcinoma. I discussed the surgical ramifications of this with the patient and his wife and I stated that, certainly the next step would be to consider a sigmoidectomy so that the whole area could be removed in its entirety. I discussed the procedure in detail with the patient, including the possible risks such as anastomotic leak which could lead to the need for reoperation and creation of a colostomy, infection, bleeding, problems with wound healing, scarring, discomfort. He did incidentally have a CT scan of the abdomen and pelvis this morning, the results of which are pending. At the conclusion of our discussion, the patient presented to me the fact that he is a frequent user of marijuana and he had done some research himself on line finding that apparently there have been some recommendations to utilize and oil supplement containing THC which have led to cancer cures. He asked my opinion in regard to this. I stated unequivocally that this was not an established medical regimen and that certainly the final decision was up to him, but pursuing this course would run the risk that his malignancy could persist, and eventually metastasize leading to an incurable situation. I again made it clear the final decision was up to him. His wife, incidentally, was quite adamant

ALLEGIANCE HEALTH
205 N. East Ave.
Jackson, MI 49201
(517) 788-4800

MR # 763001
Acct # 6882981

RE: SHARPE, STEVEN S DOB: 09/15/1959

RM: 7N 704 0

ADM: 12/08/2010 DISCH:
SURG:

David Prough, M.D.

CC: TRIMAS, ERIC DO
ULLAH, NADEEM MD

HISTORY AND PHYSICAL

HISTORY: This is a very pleasant 51-year-old male who recently underwent his first screening colonoscopy which revealed several polyps which were removed. Of concern was a 1.2 cm in diameter sessile polyp at approximately 30 cm from the anal verge which was excised and showed evidence of an intramucosal adenocarcinoma. It was felt that it was removed in its entirety, but he recently underwent a repeat colonoscopy to re-biopsy this area and also to tattoo the region. Repeat biopsies again showed residual adenoma and also intraepithelial adenocarcinoma. Patient is asymptomatic in regard to this.

PAST MEDICAL HISTORY: Negative.

PAST SURGICAL HISTORY: He had orthopaedic procedures including repair of a left leg fracture and open reduction and internal fixation for a fracture involving his left elbow following a motorcycle accident in 1976. He had bilateral inguinal herniorrhaphies in 1973.

MEDICATIONS: Tramadol, Soma.

SOCIAL HISTORY: He denies tobacco use, but is a frequent user of "medical marijuana." Drinks alcohol occasionally.

REVIEW OF SYSTEMS:
CARDIOVASCULAR: No history of atherosclerotic heart disease, no angina or shortness of breath on exertion.

GENITOURINARY: No hematuria, dysuria, urinary retention.

NEUROLOGIC: No sensory or motor problems.

about avoiding this course of unproven treatment and wished for him to proceed directly with surgical intervention. At the conclusion of our discussion, he was agreeable to be scheduled for a sigmoidectomy. I made it clear again that this was a major operation not to be taken lightly with potential serious risks, but also was probably his next best option toward ensuring and providing him the best chance that the cancer was removed in its entirety and a curable situation was reached. I also made it clear that certainly if he wished to reconsider or have the procedure canceled, this would remain his option, and to let us know should this be the case.

PLAN: The patient is scheduled for sigmoidectomy.

David Prough, M.D.
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205 N. East Ave.
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RE: SHARPE, STEVEN S DOB: 09/15/1959

RM: 7N 704 0

ADM: 12/08/2010 DISCH:
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David Prough, M.D.

CC: TRIMAS, ERIC DO
ULLAH, NADEEM MD

OPERATIVE REPORT

PREOPERATIVE DIAGNOSIS:
1. Sigmoid colon carcinoma.
2. Umbilical hernia.

POSTOPERATIVE DIAGNOSIS:
1. Sigmoid colon carcinoma.
2. Umbilical hernia.

44140 MS
49585

PROCEDURE PERFORMED:
1. Sigmoidectomy.
2. Umbilical herniorrhaphy.

SURGEON: David Prough, M.D.

ANESTHESIA: General.

ESTIMATED BLOOD LOSS: Minimal.

INDICATIONS: This is a 51-year-old male who recently, on a screening colonoscopy, was found to have a small sessile polyp in the sigmoid colon 30 cm from the anal verge. This was excised and showed evidence of an intramucosal adenocarcinoma. He underwent a repeat colonoscopy where this area was re-biopsied with the feeling that hopefully it was able to be removed for the most part endoscopically. The area was also tattooed. Repeat biopsies again showed residual adenoma and also intraepithelial adenocarcinoma. As such, a sigmoid colon resection was advised. I discussed this procedure in depth with the patient and his wife including the risks involved. He also had a small symptomatic umbilical hernia and the plan was to simultaneously repair this. They fully understood and agreed.

PROCEDURE: The patient was brought to the operating room. After general

anesthesia, his abdomen was prepped and draped in the usual sterile fashion. A midline lower abdominal incision was made and extended down through the subcutaneous tissue and anterior fascia. The posterior fascia and peritoneum was carefully entered and the incision continued in either direction. The abdomen was then explored. Both lobes of the liver were smooth and unremarkable. Gallbladder was unremarkable. Peritoneal surfaces were unremarkable. The cecum, appendix and terminal ileum were unremarkable except for being tethered in the lower pelvis by adhesions. These were taken down to allow for superior mobility of the bowel. Small bowel otherwise in the colon were unremarkable. The stained area in the lower sigmoid colon was readily identified. Retractors were appropriately positioned and small bowel and omentum were retracted superiorly. The sigmoid colon and descending colon were mobilized by incising the white line of Toldt and reflecting the colon medially up to just below the splenic flexure. The mid sigmoid colon above the area tattooed was cleared of surrounding tissue. A bowel clamp was placed proximally and a Kocher clamp distally. The intervening bowel was transected. Proceeding distally, the mesentery was sequentially clamped, divided and ligated until the lower sigmoid colon several centimeters above the pelvic floor but well beyond the tattooed area was reached. A right-angle bowel clamp was placed across the colon. Distal to this and just above this, the bowel was transected. It was taken to a bedside table and opened. The tattooed area was identified. There was a small raised remnant of a lesion consistent with the malignancy in question. There were good gross margins proximally and distally of at least several centimeters. Attention was returned intraabdominally. The two bowel ends were noted to lie comfortably end to end with no tension. A standard hand-sewn anastomosis was employed initially placing a posterior row of interrupted seromuscular 3-0 silk sutures. The inner portion of the anastomosis was then completed with a full-thickness interlocking layer of 3-0 chromic which was continued anteriorly in an inverting fashion. Anterior portion of the anastomosis was then completed with interrupted row of seromuscular 3-0 silk sutures. This created an adequate end-to-end anastomosis. Again, there was no tension. The bowel ends were clearly viable and there was a sizable palpable lumen. Mesenteric defect was closed with a figure-of-eight serosal 3-0 silk suture. Abdominal cavity was then irrigated and the return was noted to be clear. Bowel and omentum were repositioned. The small umbilical hernia was closed with a couple of figure-of-eight #1 Vicryl sutures. The midline incision was then closed by approximating the posterior fascia and peritoneum with running #1 Vicryl suture. The anterior fascia was closed with running double #1 PDS sutures. Subcutaneous tissue was closed with running 2-0 Vicryl suture and skin was approximated with staples. Final sponge and needle counts were correct. The patient

tolerated the procedure well and was taken to the recovery room in stable condition.

David Prough, M.D.
:sd002937393PROUGHD

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Allegiance Health
Formerly Doing Business as Foote Hospital
Department of Pathology
205 North East Avenue
Jackson, MI 49201
Telephone: 517-788-4951 Fax: 517-780-7295

Surgical Pathology Report

Patient Name: SHARPE, STEVEN STANLEY **Date:** 12/8/2010 **Pathology No:** S10-14299
DOB: 9/15/1959 (Age: 51) M **MRN:** 763001
Account No: 6882981 **Location:** 7N 704-0
Surgeon/Referring Physician(s): PROUGH, DAVID MD

OPERATION:
Sigmoidectomy.

TISSUE SUBMITTED:
SIGMOID COLON

CLINICAL HISTORY AND DIAGNOSIS:
Sessile polypoid lesion sigmoid colon.

(ABOVE CLINICAL INFORMATION TRANSCRIBED EXACTLY AS SUPPLIED TO THE LABORATORY)

GROSS DESCRIPTION:
SIGMOID COLON: Received in fixative is a portion of previously opened large bowel measuring 5.5 cm in length. Proximal and distal resection margins are processed in cassettes A and B. Large bowel mucosa is grey-tan and exhibits a small polypoid lesion measuring 0.4 cm coming to within 1.7 cm of the nearest surgical margin of excision. This lesion is processed in cassette C. A random representative section of grossly normal appearing large bowel mucosa is processed in cassette D. A possible lymph node dissected from pericolonic soft tissues is processed in cassette E.

djl/12/9/2010

Diane A. Hall, MD, PhD
Daniel J. La Feir, PA(ASCP)

MICROSCOPIC DESCRIPTION:
Slides examined.

FINAL PATHOLOGICAL DIAGNOSIS:

Sigmoid colon, partial sigmoidectomy:
- **Sessile tubular adenoma with residual focus of intramucosal moderately differentiated adenocarcinoma.**

Macroscopic:

Specimen Type: Partial sigmoidectomy
Specimen Length: 5.5 cm
Tumor Site: Sigmoid colon
Tumor Configuration: Sessile, exophytic

Tumor Size: 0.2 x 0.1 cm

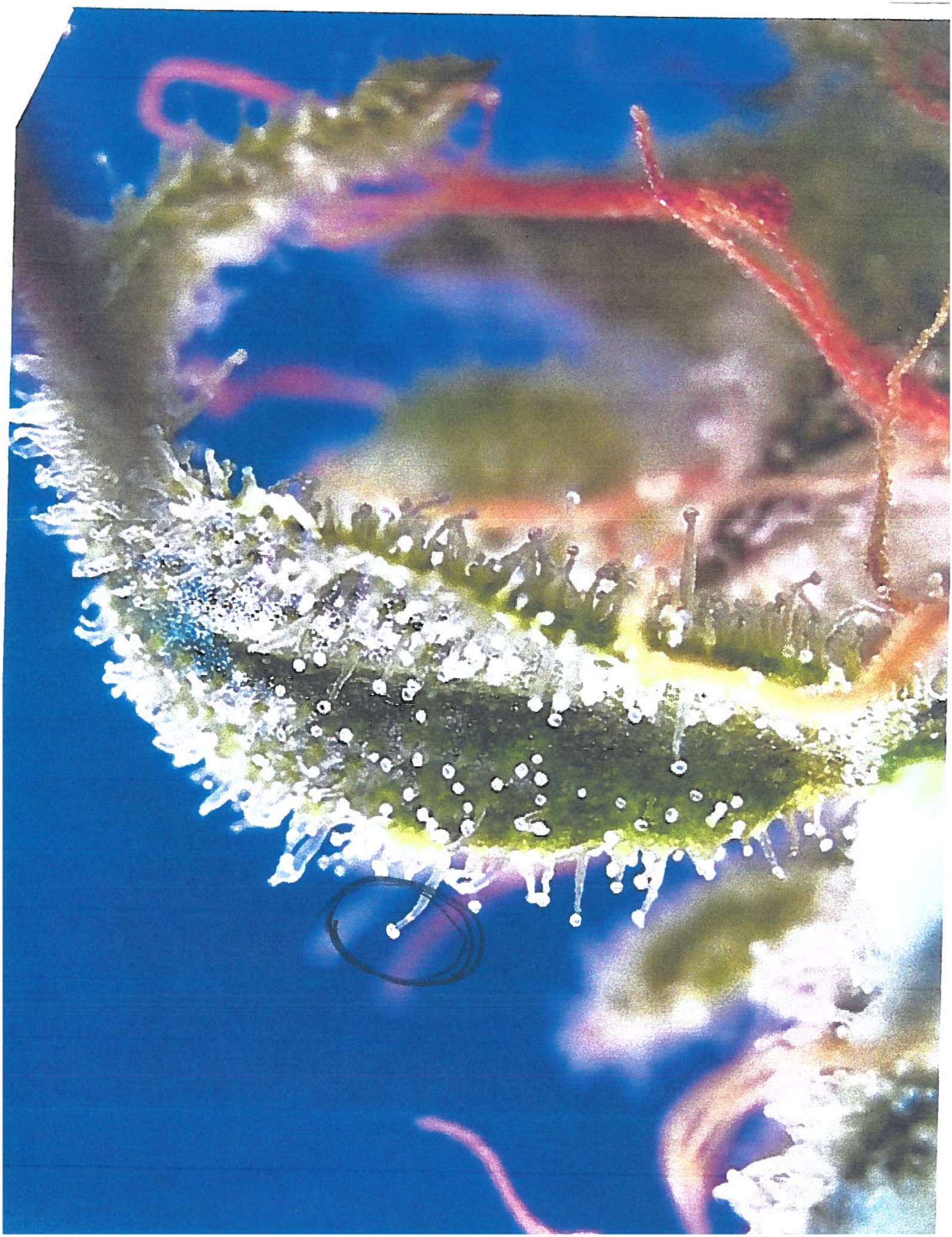
Microscopic:

Histologic Type: Invasive moderately differentiated adenocarcinoma (intramucosal adenocarcinoma)
Histologic Grade: Moderately differentiated adenocarcinoma
Margins: All surgical margins of excision-proximal, distal, radial, and serosal-are negative for adenomatous change and negative for intramucosal adenocarcinoma
Lymph Nodes: One reactive pericolonic lymph node is negative for metastatic carcinoma (note: The partial sigmoidectomy specimen was dissected in its entirety and examined with the aid of a fat clearing solution)
Vascular Space Invasion: Absent
Perineural Invasion: Absent
Tumor Border Configuration: Pushing
Intratumoral/peritumoral Lymphocytic Response: Absent
Additional Pathologic Findings: ---
Pathologic Staging (pTNM): Tis N0 MX (the intramucosal adenocarcinoma in this partial sigmoidectomy specimen lies within the mucosal lamina propria and does not extend through the muscularis mucosa into the submucosa)

(NOTE: This pathologic TNM (pTNM) classification is based only on pathologic data presently available; TNM classification is subject to revision by the patient's clinicians as additional information becomes available).

kod/12/10/2010

Kenneth O. Devaney, M.D., J.D.
Electronic Signature




You Should be Allowed to Grow your Own Medicine!
Every single one of us!
MarijuanaDoctors.com

December 2. 2013

To our honorable leaders and decision makers in Lansing.

I am the parent of a 26 year old autistic daughter who also has a sever seizure disorder. I have raised her as a single parent since she was 18 months old. The University of Michigan Neurology Department has been treating her seizure condition since she was 6 years old. The medications were working fairly well until she became a teenager and reached puberty. The medications stopped working and they have tried every combination they have available to offer and cannot get the seizures under control. What I dislike most about the medication combinations is the fact that my daughter has to have regular blood draws to make sure the medications are not affecting her liver and kidneys.

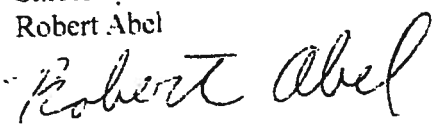
In 2008, I asked my daughters' neurologist at the University of Michigan what they thought about giving her medical marijuana. I explained to them that her caregiver would put the medical marijuana in chocolate for her to take orally as I would not teach her to smoke or vaporize the medication. The neurologists said they don't approve of anyone smoking anything and that they did not have a problem with my daughter taking the medical marijuana orally. My daughters' neurologist has been signing her paperwork every year since with the agreement that I keep them informed on her progress.

I never told my daughters school about her taking the medical marijuana because I didn't want my daughter to get into trouble with the school. Approximately 6 weeks after starting the medication my daughters teacher called to ask me if her neurologist had changed her medications. Please see the attached letter from the teacher which explains why she thought there was a medication change.

When the court system in Lansing said medables (edible medical marijuana) were now illegal I was told by a JNET officer here in Jackson that they can arrest my daughter and myself for having over the weight allowed in medical marijuana because the weight of the chocolate, or medium of your choice, is included in the weight of the edible marijuana even if there is next to no medical marijuana in the entire edible. In order to avoid the possibility of arrest I was told to stop giving my daughter her

medables. Since stopping her treatment with medical marijuana, my daughters seizures are back to the frequency and severity they were before she started taking edible medical marijuana. It is my opinion that the weight of the medable should not be a factor in determining how much is allowed to be in a person's possession, only the actual amount of the medical marijuana in the edible should be considered.

Sincerely,
Robert Abel



Kelli Abel
2060 41734

9-18-09

To Whom It May Concern:

Please scan in.

I have been working with Kelli for three years now. Kelli was having an average of three to five seizures a day. Since early June Kelli's seizures have diminished to three to five seizures a week. I have noticed that they have not been quite as strong as they had been in the past. If you have any questions please feel free to call at any time.

Thank You Sarah Dolson

Lyle Torrant Center

(517)768-5127

Kelli's father tells us that this began immediately after starting Marijuana.

R. Michael Clark
rmikeclark@gmail.com
December 2, 2013

Greetings,

Subject: Local options are necessary for Medical Marijuana patients.

I was diagnosed with Primary Progressive Multiple Sclerosis (PPMS) and Raynaud's Syndrome in 1992. I had just turned 37 years old and worked as a manager of a machine tool manufacturer. My health forced me to retire in 1998. In 2000 my feet began turning red with the feeling they were on fire. Thus began a journey to doctors of almost every specialty available to seek answers about my feet and to find some relief. In 2001 I spent 9 days at the Mayo Clinic in Rochester, MN. They confirmed the PPMS but offered no explanation for my red, burning feet except "small fiber abnormality". I left Mayo without much hope of finding relief.

Circa 2005 I began going to the University of Michigan for specialized medical care in Neurology and the Pain Clinic. In 2008 I was diagnosed with Erythromelalgia, a form of Complex Regional Pain Syndrome (CRPS). Over the years I've compiled a comprehensive list of drugs that I've tried but didn't give me any relief. I have had an Intrathecal trial in my spinal column, a Baclofen pump trial, nerve blocks and a spinal cord stimulator. Nothing gave me relief from my pain.

In 2010 my Neurologist talked me into trying medical marijuana. Marijuana doesn't take away any of my pain or even minimally reduce the burning, stabbing spasm that rolled through my left leg, but it does give me a chance to think about something other than my horrific pain. Late in 2011 I wasn't able to walk because my left foot was so painful all the time, and even more so each time I put any pressure on my foot to stand or walk. I was homebound. The pain was incredible. It never stopped and I rarely slept for more than a couple hours at a time.

Because of severe, chronic pain my left leg was amputated above the knee at the University of Michigan in February 2012. The physical pain in my left foot was gone but the hot, burning sensation was still there as Phantom Pain. It remains today as my dominant pain. About a year after amputation the searing hot pain moved into my stump and my right ankle/foot/toes are progressing to a painful end as my left side. Conventional medicines do not touch the pain. Medical marijuana is an option. I looked for a progressive, local caregiver who offered more than an ounce of weed. I met Steve Sharpe and Linda Rice through another patient who had great success with them. I called Steve and he invited me over for a lengthy conversation where he got to know me, and I him.

It is very important for me to have a local caregiver take the time to sit and talk with me about my situation and develop a plan to give me some relief. I was given samples of different strength marijuana edibles and taught how to use them. After spending days experimenting I was able to purchase exactly what I needed. My local caregiver gave me options based on our conversations and then followed my results to make sure our objective was being met. I chose

edibles which are clean and long lasting. Medical marijuana edibles give me the ability to think about something other than my pain.

I wear a prosthetic as my left leg. My pain inhibits me from walking distances over 100 feet. To get places outside our home I use a wheelchair. Inside our home I have a battery powered scooter. Each step I take is painful and somewhat awkward because of my diseased right leg/ foot/toes, painful left stump and the phantom pain on my left side.

I do not take any conventional pain medication because nothing works. I do eat medical marijuana edibles that give me a gentle body sensation and allow my mind to participate in life. With the edibles I'm able to go to meetings, engage in a conversation, have dinner with friends and laugh. I was able to get relief by working with a local caregiver who took time to know me and offered options that don't come from conventional text books. I am very grateful for safe, legal medical marijuana edibles.

Please support local Medical Marijuana caregivers as growers and suppliers.

Respectfully,

R. Michael Clark
1712 Ottawa Dr.
Jackson, MI 49203
(517) 783-2424

March 3, 2013

Dear Mr. Jarzynka,

My name is Shelley Moore & I am 48 yrs old. Over the last 9+ yrs, I have undergone 9 back surgeries, including a Spinal Cord Stimulator & a failed Morphine pump implant. My 1st surgery was to be an outpt procedure only & turned into 3 surgeries, 17 days in the hospital, a blood clot in my left leg, and the initial surgeon was fired from the practice & a different surgeon worked on me. Due to all this, I am fused from my L2-L5 S1 and my L5-S1 nerve root was amputated. The permanent nerve damage has never repaired itself. I have seen numerous Neurologists over the state of MI, including months at MSU & U of M. I have been on every narcotic & pain medication available for the constant pain in my left leg. Sitting is almost impossible, wearing shoes, any clothing that touches my leg causes great pain. Being in a vehicle is almost the worse. My life use to be constantly filled with being a Vet Tech, hunting, trapping, anything outside. My husband & I bought a 139 yr old farm house & literally gutted every board & rebuilt ourselves over 5 yrs. Now family events or even learning to do dishes is a great discomfort. I have been granted my Soc. Sec. disability now for 4 yrs as continuing working was impossible. At one point I was

taking over 9 different medications + lets not forget all the side effects of this. I didnt have much of a life. And of course, the surgeons are almost untouchable re: a law suit. I tried!

The point of this letter is to point out that I have found some relief, finally - after 9 yrs! Three years ago, I found the Compassion Club of Jackson, after the new medical Marijuana law went into effect. I had a care giver + smoked only when I had to leave house (travel) or entertain family (4 kids, 8 grandchildren) or sleep - I never abused it, I hate smoking + the effects (cancer). My doctor has worked with me re: narcotics - 1000 mg vicodin, Fentynol patches + amitriptyline. He is also very knowledgable re: Cannabis. He referred me back to the Compassion Club to inquire about topical oils, + "chocolates" made with oil. I was truely blessed that day to meet Mr. Steve Sharpe. He has been doing re-search + supplying people like me since 1998. He started in California. His passion is cancer patients. I consider myself "over the moon" lucky that he was willing to take on my case as a caregiver. He has gone above + beyond to help me get to the dose that keeps me "sane" + able to find some normalcy in my life. Again. True

ingestion of candy - I feel relief within 1/2 hour. The cannabis almost puts a "busy signal" from my brain to my leg + foot, lower spine. The pain is very distant + I get a break from the: can't focus on things, loss of memory, having the pain dictate my day. I am off my Vicodin + Fentynol also. No more upset stomach, headaches, loss of appetite, constipation + bloating.... And I don't have to smoke. Mr. Sharpe and his knowledge of how cannabis works with pain receptors has made amazing improvement in my life. I am slowly trying Yoga + Pilates at home to strengthen my "core + spine" - I am 5'5 + 110 lbs + have lost most of my prior muscle mass. I can't afford a fall + broken hip.

I pray that GOD continue to bring people like Mr. Sharpe to people like me. Until one "walks in the shoes" of myself, it's hard to convey to others what constant pain does to a person over time. It's a miserable place to be. I thank GOD every day for this blessing + Steve. Prayers really are answered. I pray that legislature + the State of Michigan come to an agreement that continues to help people with chronic pain + their families. Thank you.

Respectfully, Shelley K Moore

National Cancer Institute at the National Institutes of Health

Cannabis and Cannabinoids (PDQ®)

Health Professional Version
Last Modified: 01/17/2013

Laboratory/Animal/Preclinical Studies

Antitumor Effects
Appetite Stimulation
Analgesia

Cannabinoids are a group of 21-carbon–containing terpenophenolic compounds produced uniquely by *Cannabis sativa* and *Cannabis indica* species.[1,2] These plant-derived compounds may be referred to as phytocannabinoids. Although delta-9-tetrahydrocannabinol (THC) is the primary psychoactive ingredient, other known compounds with biologic activity are cannabinol, cannabidiol (CBD), cannabichromene, cannabigerol, tetrahydrocannabivarin, and delta-8-THC. CBD, in particular, is thought to have significant analgesic and anti-inflammatory activity without the psychoactive effect (high) of delta-9-THC.

Antitumor Effects

One study in mice and rats suggested that cannabinoids may have a protective effect against the development of certain types of tumors.[3] During this 2-year study, groups of mice and rats were given various doses of THC by gavage. A dose-related decrease in the incidence of hepatic adenoma tumors and hepatocellular carcinoma was observed in the mice. Decreased incidences of benign tumors (polyps and adenomas) in other organs (mammary gland, uterus, pituitary, testis, and pancreas) were also noted in the rats. In another study, delta-9-THC, delta-8-THC, and cannabinol were found to inhibit the growth of Lewis lung adenocarcinoma cells *in vitro* and *in vivo* .[4] In addition, other tumors have been shown to be sensitive to cannabinoid-induced growth inhibition.[5-8]

Cannabinoids may cause antitumor effects by various mechanisms, including induction of cell death, inhibition of cell growth, and inhibition of tumor angiogenesis invasion and metastasis.[9-12] One review summarizes the molecular mechanisms of action of cannabinoids as antitumor agents.[13] Cannabinoids appear to kill tumor cells but do not affect their nontransformed counterparts and may even protect them from cell death. These compounds have been shown to induce apoptosis in glioma cells in culture and induce regression of glioma tumors in mice and rats. Cannabinoids protect normal glial cells of astroglial and oligodendroglial lineages from apoptosis mediated by the CB_1 receptor.[14]

The effects of delta-9-THC and a synthetic agonist of the CB_2 receptor were investigated in

hepatocellular carcinoma (HCC).[15] Both agents reduced the viability of hepatocellular carcinoma cells *in vitro* and demonstrated antitumor effects in hepatocellular carcinoma subcutaneous xenografts in nude mice. The investigations documented that the anti-HCC effects are mediated by way of the CB2 receptor. Similar to findings in glioma cells, the cannabinoids were shown to trigger cell death through stimulation of an endoplasmic reticulum stress pathway that activates autophagy and promotes apoptosis. Other investigations have confirmed that CB1 and CB2 receptors may be potential targets in non-small cell lung carcinoma [16] and breast cancer.[17]

An *in vitro* study of the effect of CBD on programmed cell death in breast cancer cell lines found that CBD induced programmed cell death, independent of the CB1, CB2, or vanilloid receptors. CBD inhibited the survival of both estrogen receptor–positive and estrogen receptor–negative breast cancer cell lines, inducing apoptosis in a concentration-dependent manner while having little effect on nontumorigenic, mammary cells.[18]

CBD has also been demonstrated to exert a chemopreventive effect in a mouse model of colon cancer.[19] In the experimental system, azoxymethane increased premalignant and malignant lesions in the mouse colon. Animals treated with azoxymethane and CBD concurrently were protected from developing premalignant and malignant lesions. In *in vitro* experiments involving colorectal cancer cell lines, the investigators found that CBD protected DNA from oxidative damage, increased endocannabinoid levels, and reduced cell proliferation.

Another investigation into the antitumor effects of CBD examined the role of intercellular adhesion molecule-1 (ICAM-1).[12] ICAM-1 expression has been reported to be negatively correlated with cancer metastasis. In lung cancer cell lines, CBD upregulated ICAM-1, leading to decreased cancer cell invasiveness.

In an *in vivo* model using severe combined immunodeficient mice, subcutaneous tumors were generated by inoculating the animals with cells from human non-small cell lung carcinoma cell lines.[20] Tumor growth was inhibited by 60% in THC-treated mice compared with vehicle-treated control mice. Tumor specimens revealed that THC had antiangiogenic and antiproliferative effects. However, research with immunocompetent murine tumor models has demonstrated immunosuppression and enhanced tumor growth in mice treated with THC.[21,22]

In addition, both plant-derived and endogenous cannabinoids have been studied for anti-inflammatory effects. A mouse study demonstrated that endogenous cannabinoid system signaling is likely to provide intrinsic protection against colonic inflammation.[23] As a result, a hypothesis that phytocannabinoids and endocannabinoids may be useful in the risk reduction and treatment of colorectal cancer has been developed.[24-27]

Appetite Stimulation

Many animal studies have previously demonstrated that delta-9-THC and other cannabinoids have a stimulatory effect on appetite and increase food intake. It is believed that the endogenous cannabinoid system may serve as a regulator of feeding behavior. The endogenous cannabinoid anandamide potently enhances appetite in mice.[28] Moreover, CB1 receptors in the hypothalamus may be involved in the motivational or reward aspects of eating.[29]

Analgesia

Understanding the mechanism of cannabinoid-induced analgesia has been increased through the study of cannabinoid receptors, endocannabinoids, and synthetic agonists and antagonists. The CB1 receptor is found in both the central nervous system (CNS) and in peripheral nerve terminals. Similar to opioid receptors, increased levels of the CB1 receptor are found in regions of the brain that regulate nociceptive processing.[30] CB2 receptors, located predominantly in peripheral tissue, exist at very low levels in the CNS. With the development of receptor-specific antagonists, additional information about the roles of the receptors and endogenous cannabinoids in the modulation of pain has been obtained.[31,32]

Cannabinoids may also contribute to pain modulation through an anti-inflammatory mechanism; a CB2 effect with cannabinoids acting on mast cell receptors to attenuate the release of inflammatory agents, such as histamine and serotonin, and on keratinocytes to enhance the release of analgesic opioids has been described.[33-35] One study reported that the efficacy of synthetic CB1- and CB2-receptor agonists were comparable with the efficacy of morphine in a murine model of tumor pain.[36]

References

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